Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn’s Disease

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BACKGROUND
Crohn’s disease–related inflammation is characterized by reduced activity of the immunosuppressive cytokine transforming growth factor β1 (TGF-β1) due to high levels of SMAD7, an inhibitor of TGF-β1 signaling. Preclinical studies and a phase 1 study have shown that an oral SMAD7 antisense oligonucleotide, mongersen, targets ileal and colonic SMAD7.

METHODS
In a double-blind, placebo-controlled, phase 2 trial, we evaluated the efficacy of mongersen for the treatment of persons with active Crohn’s disease. Patients were randomly assigned to receive 10, 40, or 160 mg of mongersen or placebo per day for 2 weeks. The primary outcomes were clinical remission at day 15, defined as a Crohn’s Disease Activity Index (CDAI) score of less than 150, with maintenance of remission for at least 2 weeks, and the safety of mongersen treatment. A secondary outcome was clinical response (defined as a reduction of 100 points or more in the CDAI score) at day 28.

RESULTS
The proportions of patients who reached the primary end point were 55% and 65% for the 40-mg and 160-mg mongersen groups, respectively, as compared with 10% for the placebo group (P<0.001). There was no significant difference in the percentage of participants reaching clinical remission between the 10-mg group (12%) and the placebo group. The rate of clinical response was significantly greater among patients receiving 10 mg (37%), 40 mg (58%), or 160 mg (72%) of mongersen than among those receiving placebo (17%) (P=0.04, P<0.001, and P<0.001, respectively). Most adverse events were related to complications and symptoms of Crohn’s disease.

CONCLUSIONS
We found that study participants with Crohn’s disease who received mongersen had significantly higher rates of remission and clinical response than those who received placebo. (Funded by Giuliani; EudraCT number, 2011-002640-27)
Crohn's disease is a chronic inflammatory illness that primarily affects the terminal ileum and right colon. Crohn's disease–related inflammation is segmental and transmural, leading to various degrees of tissue damage. At disease onset, most patients have inflammatory lesions, which become predominantly strictures or penetrating lesions over time. Mucosal healing can be promoted with the use of immunosuppressive drugs and anti–tumor necrosis factor α (TNF-α) antibodies; however, more than one third of patients do not have a response to these therapies. The efficacy of these drugs may also diminish over time, and they can increase a patient’s risk of opportunistic infections and cancer. Therefore, there is a need for novel drugs that target the major inflammatory pathways in Crohn's disease.

The gut inflammation associated with Crohn's disease is characterized by abnormal decreases in the activity of the immunosuppressive cytokine transforming growth factor (TGF–β1). This is caused by increased levels of SMAD7, an intracellular protein that binds TGF-β receptor and prevents TGF-β1–associated and SMAD-associated signaling. Consequently, SMAD7 is a potential target for suppression of Crohn's disease–associated inflammation.

Mongersen (formerly GED0301) is a formulation containing a 21-base single-strand phosphorothioate oligonucleotide that hybridizes to the human SMAD7 messenger RNA (mRNA) and facilitates RNase H–mediated RNA degradation through a classic antisense mechanism. Mongersen was developed in a proprietary modified-release tablet designed to deliver the active substance primarily into the lumen of the terminal ileum and right colon. This is achieved through the pH-dependent coating of the tablet, which consists of methacrylic acid–ethyl acrylate copolymers.

Mongersen has previously been shown to down-regulate Smad7 and prevent and alleviate Crohn's disease–like colitis in mice. Studies conducted with mucosal cells from humans with Crohn's disease showed that inhibition of SMAD7 production by mongersen restored TGF-β1 signaling, thereby suppressing inflammatory cytokine production (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In a phase 1 study involving 15 patients with active Crohn's disease, we observed a clinical response (defined as a decrease of >70 points in the Crohn's Disease Activity Index [CDAI] score) in all participants 8 days after the first dose of mongersen; there was also evidence of a durable effect of the drug. Pharmacokinetic analysis of plasma before and after treatment suggested that mongersen was not systemically available; it was detectable in the plasma of one participant at a level only marginally above the lower limit of quantification. Therefore, we sought to better define the efficacy and safety of mongersen for treating adults with active Crohn's disease.

**Methods**

**Patients**

We enrolled patients (18 to 75 years of age) who had moderate-to-severe Crohn's disease (CDAI score of 220 to 400; scores can range from 0 to 600, with higher scores indicating greater disease activity) 1 week or more before enrollment, with inflammatory lesions in the terminal ileum, right colon, or both, as documented with the use of ileocolonoscopy and contrast ultrasonography of the small intestine, magnetic resonance enterography, or computed tomographic enterography within 1 year before enrollment, and had steroid-dependent or glucocorticoid-resistant disease, as defined by guidelines of the European Crohn's and Colitis Organization.

Because the active compound of mongersen is released in the terminal ileum and right (proximal) colon, we excluded patients with known lesions in the stomach, proximal small intestine, transverse colon, or left colon. Patients were also excluded if they had strictures, fistulae, perianal disease, extraintestinal symptoms, active or recent infections, or a history of cancer.

Patients could continue to receive stable doses of oral prednisolone (≤40 mg per day), budesonide (≤9 mg per day), or mesalamine during the 2-week treatment period; they could also receive a stable dose of immunomodulators (e.g., azathioprine, mercaptopurine, or methotrexate) if therapy had been initiated 6 or more months before initiation of the study treatment. Antibiotic agents, glucocorticoids, immunosuppressive drugs, and biologics could not be initiated before study entry or during the 2-week treatment period.

Patients received no treatment with anti–TNF-α antibodies or other biologic agents within 90 days
or antibiotics within 3 weeks before the date of their enrollment in the trial. Female participants used two forms of contraception throughout the study. We excluded women who were pregnant or breast-feeding, as well as persons with previous proctocolectomy or intestinal resection resulting in the short-bowel syndrome and persons with a clinically significant abnormality on electrocardiography or laboratory testing. Patients who had worsening of disease (increase of ≥70 points in the CDAI score) could receive rescue therapy with biologic agents, immunosuppressive drugs, or both after the 2-week treatment period, and for those who were in clinical remission after the 2-week treatment period (CDAI score <150 at both day 15 and day 28), glucocorticoids could be tapered.

The study protocol was approved by the institutional review board or ethics committee at each of the 17 study centers in Italy and Germany. Written informed consent was obtained from patients before they underwent screening for eligibility (Table S1 in the Supplementary Appendix). Eligible patients underwent randomization between September 2011 and June 2013.

**Mongersen**

Mongersen is a 21-base oligonucleotide with the sequence 5′-GTC GCC CCT TCT CCC CGC AGC-3′. The phosphorothioate chemistry consists of replacement of a nonbonding oxygen with a sulfur atom in each of the internucleotide linkages. The cytosine residues at nucleotide positions 3 and 16 are modified by 5-methylation.

**STUDY DESIGN**

In this multicenter, randomized, placebo-controlled, double-blind, phase 2 clinical trial, patients were randomly assigned to receive one of three doses of mongersen (10, 40, or 160 mg per day) or placebo in a 1:1:1:1 ratio by means of a computer-generated randomization schedule without stratification or block allocation. The placebo and active drug were identical in appearance and taste. The three doses of mongersen and the treatment duration were selected on the basis of preclinical, toxicologic, and phase 1 studies.\(^9,11\)

Patients received treatment daily for 2 weeks and were evaluated at days 15, 28, and 84.

The study was sponsored by Giuliani, acting under contract to Nogra Pharma; employees of Giuliani collected and had access to the data, participated in its analysis, and participated in discussions about its interpretation. The study was designed by the first author, who also wrote the first draft of the manuscript; all authors contributed equally to the gathering and analysis of data, and each author had access to the full data set. Editorial assistance with the preparation of the manuscript for resubmission was received from an editor (from Precise Publications) and from Peloton Advantage; both were supported by Celgene, which had no additional role in the study. The authors vouch that the study was conducted in accordance with the protocol and statistical analysis plan, both of which are available at NEJM.org. Each author vouches for the accuracy and completeness of the reported data, and each author agreed with the decision to submit the final version for publication.

**EFFICACY AND SAFETY ASSESSMENT**

The primary end point of the study was the percentage of patients who were in remission at day 15 (defined as a CDAI score of <150) and who remained in remission for at least 2 weeks.\(^14\)

Evaluation of the safety of mongersen treatment was another objective. Clinical, biochemical, and hematologic variables were assessed on days −7, 1, 15, 28, and 84. An enzyme-linked immunosorbent assay (ELISA) was used to monitor the patients for complement activation (a side effect of systemic antisense exposure)\(^3\). The severity of adverse events and their cause (study drug or procedure) were determined.

Secondary end points included the rates of clinical response, defined as a decrease in the CDAI score of 100 points or more or a decrease of 70 points or more, at days 15 and 28, as well as the percentages of patients with a CDAI score of less than 150 at days 15, 28, and 84. We also assessed the CDAI score before treatment and during the week preceding days 15, 28, and 84, as well as changes in median CDAI scores from baseline to each time point. Percentages of patients who had normalization of C-reactive protein after treatment, had elevated C-reactive protein levels at baseline and reached clinical remission, and were in glucocorticoid-free remission at day 84 were also evaluated. Additional end points included changes in plasma levels of proinflammatory cytokines (e.g., interleukin-8 and TNF-α), measured with the use of commercial ELISA kits (R&D Systems).
STATISTICAL ANALYSIS
Sample size was determined with the use of a one-sided testing framework with an alpha error of 0.1 and a beta error of 0.1, because the prospective primary hypothesis was that 14 days of treatment with the highest mongersen doses (40 and 160 mg per day) would result in a higher proportion of patients in clinical remission than would 14 days of placebo treatment and that the lowest dose of mongersen (10 mg per day) would not be effective. Rates of remission were assumed to be 50% with the highest mongersen doses and 20% with placebo. It was estimated that 40 patients per group would be needed for the study to have at least 90% power to detect significant differences in remission rates between one of the two groups treated with the highest mongersen doses and the placebo group. All efficacy analyses were conducted according to the intention-to-treat principle with all patients who underwent randomization and who received at least one dose of study medication. Patients with missing primary end-point data at day 15 or week 4 were classified as not having a response. Patients who received rescue therapy because of worsening of disease after day 28 were classified as not having a response for the secondary end-point analyses. Missing data for continuous end points and secondary variables were imputed with the use of the last-observation-carried-forward method.

The primary efficacy and adverse-event analyses included all 166 randomly assigned and treated patients. Remission and response rates were compared with the use of Pearson’s chi-square test or, when not applicable, with Fisher’s exact test. Although sample size was determined with the use of a one-sided testing framework, we present results in the conventional two-sided framework. We compared each of the three treatment groups with the placebo group and each group treated with either 160 or 40 mg per day of the drug with the 10-mg dose group.

Demographic characteristics, rates of adverse events, and proportions of patients who discontinued glucocorticoid treatment were compared with the use of descriptive methods. Proportions of patients with changes from baseline in the C-reactive protein level were also documented. Changes in median CDAI scores and cytokine levels from baseline to each time point were analyzed with the Mann-Whitney test and Student’s t-test, respectively.

RESULTS
CHARACTERISTICS OF THE PATIENTS
Among 188 screened patients, 166 were eligible for participation in the study and were randomly assigned to receive one of three mongersen doses or placebo (Fig. S2 in the Supplementary Appendix). Demographic and baseline disease characteristics were generally similar among the groups, with the exception that CDAI scores were higher in the 40-mg group than in the placebo group and Crohn’s disease duration was longer in the 40-mg group and the 160-mg group than in the placebo group (Table 1). Of the 166 patients who underwent randomization and received at least one dose of study medication, 6 had protocol violations and missing data at day 15 and were classified as not being in remission (CDAI score ≥150) in the analysis of the primary end point (Fig. S2 in the Supplementary Appendix). A total of 160 patients (96.4%) completed the 2 weeks of treatment and the day 28 follow-up, and 138 patients (83.1%) completed the day 84 follow-up. The reasons for withdrawal from the study after day 28 are indicated in Figure S2 in the Supplementary Appendix. In particular, 6 patients (2 assigned to placebo, 1 assigned to 10 mg of mongersen per day, and 3 assigned to 160 mg of mongersen per day) received rescue therapy with biologic agents or immunosuppressive drugs because of a worsening of disease after day 28 and were classified as not having a response (CDAI score ≥150) in the analysis of the secondary end points.

CLINICAL REMISSION AND RESPONSE
The proportions of patients with clinical remission (defined as a CDAI score of <150 at day 15 and maintenance of a CDAI score of <150 until day 28) were significantly higher in the 160-mg group (65%) and 40-mg group (55%) than in the 10-mg group (12%; P < 0.001) and placebo group (10%; Fig. 1A). No significant differences between the 160-mg group and the 40-mg group or between the 10-mg group and the placebo group were observed (Fig. 1A).

The proportions of patients who had a 100-point clinical response at day 15 were significantly greater in the 160-mg and 40-mg groups than in the 10-mg group (P < 0.001 and P = 0.03, respectively, in a two-sided test) and in the 160-mg group than in the placebo group (P < 0.001) (Fig. 1B).
No significant difference was observed between the 40-mg group and the placebo group.

At day 28, the proportions of patients with a 100-point clinical response (i.e., a CDAI score reduction of ≥100 points) were significantly higher in the 160-mg group (72%), 40-mg group (58%), and 10-mg group (37%) than in the placebo group (17%) (Fig. 1C). The percentages of patients with CDAI score reductions of 70 points or more at days 15 and 28 were significantly greater with the higher mongersen doses than with the lower dose or with placebo (Fig. S3A and S3B in the Supplementary Appendix).

The proportions of patients who had a CDAI score of less than 150 at days 15, 28, and 84 were significantly higher in the 160-mg group and 40-mg group than in the 10-mg group and the placebo group (Fig. S4 in the Supplementary Appendix). We found no significant differences between the 160-mg group and the 40-mg group or between the 10-mg group and the placebo group (Fig. S4 in the Supplementary Appendix).

### Changes in Clinical and Inflammatory Measures

The median changes in the CDAI score in the 40-mg and 160-mg groups were significantly greater than the change in the placebo group at each time point (Table S2 in the Supplementary Appendix). No significant difference was seen between the 10-mg group and the placebo group at any time point (Table S2 in the Supplementary Appendix).

Overall, 102 of 166 patients (61.4%) had an elevated C-reactive protein level (i.e., >3 mg per liter) at screening (Fig. S5A in the Supplementary Appendix).

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**Table 1. Baseline Demographic and Clinical Characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N = 42)</th>
<th>10 mg (N = 41)</th>
<th>40 mg (N = 40)</th>
<th>160 mg (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range) — yr</td>
<td>41 (19–74)</td>
<td>43 (20–71)</td>
<td>43 (19–69)</td>
<td>43 (22–70)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>23 (55)</td>
<td>17 (41)</td>
<td>21 (52)</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>19 (45)</td>
<td>24 (59)</td>
<td>19 (48)</td>
<td>23 (53)</td>
</tr>
<tr>
<td>Mean BMI (range)†</td>
<td>23.2 (15.8–39.8)</td>
<td>22.2 (15.9–29.9)</td>
<td>23.6 (18.3–38.4)</td>
<td>23.6 (15.1–36.4)</td>
</tr>
<tr>
<td>Median Crohn’s Disease Activity Index score (range)</td>
<td>264 (222–392)</td>
<td>246 (221–399)</td>
<td>240 (223–368);‡</td>
<td>243 (221–396)</td>
</tr>
<tr>
<td>Mean C-reactive protein level (range) — mg/liter</td>
<td>5.1 (0–102)</td>
<td>4.3 (0–78)</td>
<td>4.9 (0–47)</td>
<td>4.6 (0–51)</td>
</tr>
<tr>
<td>Glucocorticoid-dependent disease — no. (%)</td>
<td>36 (86)</td>
<td>32 (78)</td>
<td>38 (95)</td>
<td>36 (84)</td>
</tr>
<tr>
<td>Glucocorticoid-resistant disease — no. (%)</td>
<td>6 (14)</td>
<td>9 (22)</td>
<td>2 (5)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Taking glucocorticoids at enrollment — no. (%)</td>
<td>9 (21)</td>
<td>7 (17)</td>
<td>13 (32)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Taking concomitant immunomodulators — no. (%)</td>
<td>12 (29)</td>
<td>6 (15)</td>
<td>10 (25)</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Current smoker — no. (%)</td>
<td>14 (33)</td>
<td>18 (44)</td>
<td>13 (32)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>History of Crohn’s disease–related intestinal resection — no. (%)</td>
<td>14 (33)</td>
<td>21 (51)</td>
<td>15 (38)</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Duration of Crohn’s disease — yr</td>
<td>10.9±1.4</td>
<td>12.3±1.6</td>
<td>7.0±1.3¶</td>
<td>9.3±1.5¶</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SE.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
‡ P = 0.04 for the comparison with the placebo group.
¶ P = 0.01 for the comparison with the placebo group.
© P = 0.02 for the comparison with the placebo group.
Appendix); among the patients who had elevated C-reactive protein levels at baseline, the proportions with normalization of these levels at day 15 were 4% in the placebo group, 22% in the 10-mg group, 18% in the 40-mg group, and 18% in the 160-mg group (Fig. S5B in the Supplementary Appendix). Among patients with an elevated C-reactive protein level at baseline, neither placebo nor mongersen treatment significantly reduced the median C-reactive protein level at days 15, 28, or 84 (Table S3 in the Supplementary Appendix).

In the subgroup of patients with baseline elevations in the C-reactive protein level, the rates of remission in the 160-mg and 40-mg groups were significantly greater than the rate in the placebo group; there were no significant differences between these two higher dose groups or between the 10-mg group and the placebo group (Fig. S6 in the Supplementary Appendix). The response rates were similar among patients with an elevated C-reactive protein level and patients with a normal C-reactive protein level at baseline. The proportions of patients with baseline elevations in the C-reactive protein level who had remission (defined as a CDAI score of <150 and a normalized C-reactive protein level) at day 15 were 17% (1 of 6) in the placebo group, 0% (0 of 4) in the 10-mg group, 18% (2 of 11) in the 40-mg group, and 25% (5 of 20) in the 160-mg group.

No significant differences in the median dose of glucocorticoids were detected among the groups at baseline (Table 1). One patient in the placebo group and 1 patient in the 10-mg group were taking 25 mg of prednisone per day, and 1 patient in the 40-mg group was taking 5 mg of prednisone per day. Budesonide was taken by 8 patients in the placebo group (median dose, 6 mg per day), 6 patients in the 10-mg group (median dose, 6 mg per day), 12 patients in the 40-mg group (median dose, 6 mg per day), and 9 patients in the 160-mg group (median dose, 7.5 mg per day). At day 84, the percentage of patients who had a glucocorticoid-free remission was significantly greater in
The new england journal of medicine

The New England Journal of Medicine

March 19, 2015

The new england journal of medicine

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the 160-mg group than in the placebo group (6 of 9 [67%] vs. 1 of 9 [11%], P=0.04), and there was no significant difference between the 10-mg group (3 of 7, 43%) or the 40-mg group (6 of 13, 46%) and the placebo group (1 of 9, 11%).

Treatment with 40 mg or 160 mg of mongersen per day but not with 10 mg per day significantly reduced the mean concentration of interleukin-8 and TNF-α in plasma. This effect was evident at day 15 and day 28 (Table S4 in the Supplementary Appendix).

**SAFETY AND ADVERSE EVENTS**

Nine serious adverse events were reported, in six patients (Table 2). Most serious adverse events were hospitalizations for complications or symptoms of Crohn’s disease (Table 2). There were no deaths.

Adverse events occurring during or after treatment in more than 5% of patients in any study group are shown in Table 3. Most adverse events were mild (64% in the placebo group and 65% in the combined mongersen groups) (Table 3, and Tables S5 and S6 in the Supplementary Appendix). We did not observe changes in the levels of serum complement factors.

**DISCUSSION**

Targeting SMAD7 with mongersen was of clinical benefit for study participants with active Crohn’s disease. The effect was rapid in onset and durable in many patients. The rates of remission were greater in the groups of patients treated with 40 mg or 160 mg of mongersen per day than in the groups receiving 10 mg per day or placebo and were similar to the remission rates achieved in some other phase 2 trials of new drugs for the treatment of Crohn’s disease, which range from 16% to 48%, as well as to remission rates in phase 3 trials of existing therapies. All three groups receiving mongersen had a significantly greater rate of clinical response than did the placebo group, which suggests that even a dose of 10 mg per day may be therapeutic in a subset of patients. Direct head-to-head studies are required to ascertain the benefit of mongersen relative to other currently available drugs in inducing and maintaining remission in Crohn’s disease.

Normalization of C-reactive protein levels was more common in each of the three groups of patients treated with mongersen than in the placebo group, although the differences in the numbers of participants in whom normalization was achieved were not significant. Although the absence of an association between improvement in the CDAI score and normalization of the C-reactive protein level in all the patients treated with mongersen remains to be clarified, it is conceivable that healing of tissue lesions, normalization of C-reactive protein levels, or both require treatment for longer than 2 weeks. Nearly 40% of patients had normal C-reactive protein levels at baseline, possibly because our study population included only patients with inflammatory lesions restricted to the terminal ileum and right colon. Although Crohn’s ileitis is frequently associated with low or normal C-reactive protein levels, patients with elevated levels at baseline had a superior response with 40 mg or 160 mg of mongersen than with placebo. Our findings also indicate that the induction of remission was not affected by the baseline level of C-reactive protein.

A diminished ability to mount an efficient counterregulatory TGF-β1 response to inflammatory stimuli is believed to be instrumental in

Table 2. Serious Adverse Events Registered during the Study.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 42)</th>
<th>Mongersen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg (N = 41)</td>
<td>40 mg (N = 40)</td>
</tr>
<tr>
<td>Patients with at least one serious adverse event — no. (%)</td>
<td>1 (2)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Serious adverse events — no. (%)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Patients with serious adverse event — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Seton placement for perianal fistula</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Worsening of Crohn’s disease</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Surgery for hemorrhoid thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Thermal burn</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

* The differences between groups were not significant.
the pathogenesis of Crohn's disease. This role of TGF-β1 in intestinal immune homeostasis is dramatically evident in studies in mice. Mice lacking TGF-β1 or expressing a functionally inactive form of TGF-βRII on T cells have excessive activation of effector T cells and spontaneous development of gut inflammation.21,22 Neutralization of endogenous TGF-β1 in wild-type mice also leads to severe colitis.23 Conversely, boosting of TGF-β1 activity is associated with complete protection from the development of colitis or a reduction in the severity of colitis.24,25 The dosage effects that we observed are probably related to the amount of active compound delivered to the gut and thus the extent to which SMAD7 is down-regulated and TGF-β1–dependent counterregulatory signals are up-regulated.9,24

The percentages of patients with a CDAI score of less than 150 at week 4 were greater than those seen at the end of the treatment period (i.e., day 14), and the clinical benefit induced by 2 weeks of treatment with mongersen persisted over time; at the end of follow-up, 29%, 62%, and 67% of patients treated with 10, 40, and 160 mg per day of mongersen, respectively, had CDAI scores of less than 150. We have no data on the intestinal distribution of orally administered mongersen in persons with Crohn's disease, but because orally administered mongersen disappears quickly from the gut of mice with experimentally induced colitis, we suggest that the durable effect is unlikely to be related to drug accumulation in the gut.9 Moreover, intact mongersen was evaluated in tissue and plasma samples from mice and cynomolgus monkeys with the use of a hybridization-type assay.9 On oral administration of multiple, large clinical doses, mongersen was detectable in liver and kidney (the known major organs of oligonucleotide uptake when doses are given systemically) but at levels that were hundreds of times lower than when mongersen was administered by intravenous or subcutaneous injection. This is consistent with the very low plasma levels of mongersen reported in an earlier phase 1 study.11 The therapeutic effect of mongersen requires not only knockdown of SMAD7 but also reestablishment of TGF-β1–dependent suppression of multiple mucosal cell types.8,30,24

We did not identify safety issues with the oral administration of mongersen in patients with active Crohn's disease, to the extent that a 2-week trial of the drug in 124 persons can determine safety.11,12 The majority of serious adverse events reported were related to complications or symptoms of Crohn's disease.

Ideally, further clinical study of mongersen for Crohn's disease should determine the most beneficial clinical dosage regimen, test longer durations of treatment, and assess mucosal healing on the basis of endoscopic analyses of the study participants. Ileocolonoscopy was optional in the current study, and no patients agreed to undergo ileocolonoscopy at the end of the study. Longer-term studies of the efficacy and safety of mongersen, its comparison with existing therapies, and its effect on mucosal healing are needed. Further work will also be needed to determine whether longer-term treatment with or higher doses of mongersen increase the risk of fibrosis, given the profibrogenic role of TGF-β1 in many organs.26

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 42)</th>
<th>Mongersen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg (N = 41)</td>
<td>40 mg (N = 40)</td>
</tr>
<tr>
<td>Patients with at least one adverse event — no. (%)</td>
<td>28 (67)</td>
<td>20 (49)</td>
</tr>
<tr>
<td>Adverse events — no.</td>
<td>64</td>
<td>39</td>
</tr>
<tr>
<td>Patients with adverse event — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (14)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Worsening of Crohn's disease</td>
<td>13 (31)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>C-reactive protein level increased</td>
<td>4 (10)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (10)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (2)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (2)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>3 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Increased aminotransferase levels</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Adverse events that occurred in less than 5% of the patients are reported in the Supplementary Appendix.
Antisense oligonucleotides targeting mRNA have been used to treat chronic inflammatory diseases. Antisense oligonucleotides against mRNA encoding the intercellular adhesion molecule 1 (ICAM-1), administered intravenously, have been tested with no success in patients with Crohn's disease.27,28 Perhaps oral formulations with local activity are more effective than systemic formulations (i.e., subcutaneous) in allowing the antisense compound to reach the diseased tissue.

In conclusion, the data from this phase 2 study provide evidence of the efficacy and adverse-effect profile of mongsersen in active Crohn's disease. Our results support earlier work showing that SMAD7 has a role in the inflammatory reaction of Crohn's disease.8,10,28 Supported by Giuliani, acting under contract to Nogra Pharma, Milan.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Nicole Cooper (Precise Publications), Jennifer Sch-winn, and Peloton Advantage for editorial assistance.

APPENDIX

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SMAD7 Antisense Oligonucleotide in Crohn’s Disease


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